

(19) World Intellectual Property  
Organization  
International Bureau



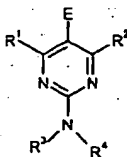
(43) International Publication Date  
1 July 2004 (01.07.2004)

PCT

(10) International Publication Number  
WO 2004/054986 A3

- (51) International Patent Classification<sup>7</sup>: C07D 239/42, 239/22
- (21) International Application Number: PCT/GB2003/005359
- (22) International Filing Date: 9 December 2003 (09.12.2003)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:  
0229243.1 16 December 2002 (16.12.2002) GB  
0303589.6 17 February 2003 (17.02.2003) GB  
0318515.4 7 August 2003 (07.08.2003) GB
- (71) Applicant (for all designated States except US): ASTRAZENEKA UK LIMITED [GB/GB]; 15 Stanhope Gate, London W1K 1LN (GB).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): NEWTON, Lee [GB/GB]; Earls Road, Grangemouth, Stirlingshire FK3 8XG (GB). BAILEY, Mark [GB/GB]; Earls Road, Grangemouth, Stirlingshire FK3 8XG (GB).
- (74) Agent: BILL, Kevin; AstraZeneca, R & D Headquarters, Global Intellectual Property, Patents, SE-151 85 Sodertälje (SE).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (regional): ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW); Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM); European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR); OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:  
— with international search report
- (88) Date of publication of the international search report:  
2 December 2004
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PROCESS FOR THE PREPARATION OF PYRIMIDINE COMPOUNDS



(I)

(57) Abstract: A process for the preparation of a compound of Formula (I) and intermediates useful therein are provided. The process comprises reacting a compound of formula  $R^1\text{-CO-CH}_2\text{-E}$  with a compound of formula  $R^2\text{-CHX}^1\text{X}^2$  in the presence of a compound of formula  $R^3\text{R}^4\text{N-C(=NH)NH}_2$  and a catalyst, thereby to form a dihydropyrimidine; and oxidising the dihydropyrimidine to form the compound of Formula (I).  $R^1$  is H or an alkyl group;  $R^2$  is H, an alkyl or aryl group;  $R^3$  and  $R^4$  are each independently H, alkyl or aryl, or  $R^3$  and  $R^4$  are linked to form, together with the nitrogen to which they are attached to form a 5 to 7 membered heterocyclic ring; E is H, an unsubstituted alkyl group, an aryl group or an electron withdrawing group; and  $X^1$  and  $X^2$  are each independently leaving groups, or  $X^1$  and  $X^2$  together represent =O.

BEST AVAILABLE COPY

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 03/05359

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 C07D239/42 C07D239/22

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data, PAJ

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WATANABE M ET AL: "SYNTHESIS AND BIOLOGICAL ANTIVITY OF METHANESULFONAMIDE PYRIMIDINE-AND N-METHANESULFONYL PYRROLE-SUBSTITUTED 3,5-DIHYDROXY-6-HEPTENOATES, A NOVEL SERIES OF HMG-COA REDUCTASE INHIBITORS" BIOORGANIC & MEDICINAL CHEMISTRY, ELSEVIER SCIENCE LTD, GB, vol. 5, no. 2, 1997, pages 437-444, XP000882043 ISSN: 0968-0896 Scheme 1	1-9, 19-26
A	WO 01/04100 A (LONZA AG ;VEITH ULRICH (CH)) 18 January 2001 (2001-01-18) cited in the application the whole document	1-26
	-/--	

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"Z" document member of the same patent family

Date of the actual completion of the international search

7 April 2004

Date of mailing of the international search report

07. 09. 04

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl  
Fax: (+31-70) 340-3016

Authorized officer

Zellner, A

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 03/05359

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 521 471 A (SHIONOGI & CO) 7 January 1993 (1993-01-07) cited in the application the whole document	1-26
A	BREAUX E J ET AL: "An improved general synthesis of 4-aryl-5-pyrimidinecarboxylates" JOURNAL OF HETEROCYCLIC CHEMISTRY, HETEROCORPORATION. PROVO, US, vol. 18, January 1981 (1981-01), pages 183-184, XP002117468 ISSN: 0022-152X the whole document	1-9, 19-24
X	VANDEN EYNDE, J. J. ET AL: "Microwave-mediated regioselective synthesis of novel pyrimido[1,2- a]pyrimidines under solvent-free conditions" TETRAHEDRON (2001), 57(9), 1785-1791, XP002276336 page 1786, line 1 page 1789; examples 4.3.1-4.3.2	10-13, 15,16
P,X	DE LUCA, LIDIA ET AL: "Cellulose Beads: a New Versatile Solid Support for Microwave-Assisted Synthesis. Preparation of Pyrazole and Isoxazole Libraries" JOURNAL OF COMBINATORIAL CHEMISTRY (2003), 5(4), 465-471, XP002276337 p. 466, col. 2, Scheme 3, compound 3 RN 575838-12-9	25,26

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/GB 03/05359

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
  
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
  
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
  
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:  
1-9, 19-26

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-9,19-26

A process for the preparation of compounds of formulae (1) and (3) and a compound according to claims 25 and 26.

---

2. claims: 10-18

A compound of formula (2a) and a process for its preparation.

---

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 03/05359

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0104100 - A	18-01-2001	AU 6266600 A	30-01-2001
		CA 2378782 A1	18-01-2001
		CN 1370151 T	18-09-2002
		CZ 20020061 A3	15-05-2002
		WO 0104100 A1	18-01-2001
		EP 1194414 A1	10-04-2002
		HU 0202006 A2	28-12-2002
		JP 2003504359 T	04-02-2003
		NO 20020163 A	11-01-2002
		PL 353058 A1	06-10-2003
		SK 222002 A3	04-06-2002
		US 6579984 B1	17-06-2003
		US 2003199695 A1	23-10-2003
EP 0521471 A	07-01-1993	AT 197149 T	15-11-2000
		CA 2072945 A1	02-01-1993
		CY 2226 A	18-04-2003
		DE 69231530 D1	30-11-2000
		DE 69231530 T2	13-06-2001
		DK 521471 T3	05-02-2001
		EP 0521471 A1	07-01-1993
		ES 2153824 T3	16-03-2001
		GR 3035189 T3	30-04-2001
		HK 1011986 A1	13-07-2001
		HU 220624 B1	28-03-2002
		HU 61531 A2	28-01-1993
		JP 2648897 B2	03-09-1997
		JP 5178841 A	20-07-1993
		KR 9605951 B1	06-05-1996
		LU 91042 A9	24-11-2003
		NL 300125 I1	01-07-2003
		PT 521471 T	30-04-2001
		US RE37314 E1	07-08-2001
		US 5260440 A	09-11-1993

**This Page is Inserted by IFW Indexing and Scanning  
Operations and is not part of the Official Record**

**BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☒ BLACK BORDERS
- ☒ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☒ GRAY SCALE DOCUMENTS
- ☒ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☒ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: \_\_\_\_\_

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.**